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Appendix A

Data Sources

libid	name	tissue	histology	protocol
33286	Stratagene liver (#937224)	liver	normal	n.n.
33313	Stratagene fetal spleen (#937205)	spleen	normal	n.n.
33318	Soares adult brain N2b5HB55Y	brain	normal	u.c.
33320	Soares ovary tumor NbHOT	ovary	neoplasia	n.n.
33401	Stratagene endothelial cell 937223	vascular	normal	n.n.
33405	Stratagene muscle 937209	muscle	normal	n.n.
33628	HM3	muscle	normal	n.n.
33664	normal human trabecular bone cells	bone	normal	n.n.
34182	NIH_MGC_7	lung	neoplasia	n.n.
34184	NIH_MGC_8	lymph node	neoplasia	n.n.
34185	NIH_MGC_14	kidney	neoplasia	n.n.
34186	NIH_MGC_15	colon	neoplasia	n.n.
34187	NIH_MGC_20	skin	neoplasia	m.t.
34188	NIH_MGC_21	placenta	neoplasia	n.n.
34284	NIH_MGC_37	lymph node	normal	n.n.
34300	NIH_MGC_17	muscle	neoplasia	n.n.
34317	NIH_MGC_9	ovary	neoplasia	n.n.
34333	NIH_MGC_16	eye	neoplasia	n.n.
34334	NIH_MGC_19	brain	neoplasia	n.n.
34347	NIH_MGC_50	lymph node	normal	n.n.
34619	NIH_MGC_39	pancreas	neoplasia	n.n.
34620	NIH_MGC_44	uterus	neoplasia	n.n.
35023	NIH_MGC_53	genitourinary	neoplasia	n.n.
35026	NIH_MGC_56	brain	normal	n.n.
35029	NIH_MGC_59	salivary gland	neoplasia	n.n.
35031	NIH_MGC_61	testis	neoplasia	n.n.
35614	NIH_MGC_76	liver	normal	n.n.
35615	NIH_MGC_81	muscle	normal	n.n.
35623	GLC	liver	normal	u.c.
35627	NIH_MGC_68	lung	neoplasia	n.n.
35629	NIH_MGC_70	pancreas	neoplasia	n.n.
35639	NIH_MGC_18	lung	neoplasia	n.n.
35645	NIH_MGC_46	uterus	neoplasia	n.n.
35646	NIH_MGC_48	lymph node	normal	n.n.
37458	GKC	liver	neoplasia	u.c.
37694	CB	lymphoreticular	normal	u.c.

libid	name	tissue	histology	protocol
37853	PLACE1	placenta	normal	u.c.
37900	NIH_MGC_85	lymph node	neoplasia	n.n.
37946	NIH_MGC_49	skin	neoplasia	n.n.
37948	NIH_MGC_43	eye	normal	n.n.
37949	NIH_MGC_42	pancreas	neoplasia	n.n.
39275	NIH_MGC_40	prostate	neoplasia	n.n.
39276	NIH_MGC_41	skin	neoplasia	n.n.
39336	NIH_MGC_98	brain	neoplasia	n.n.
39339	NIH_MGC_99	lymphoreticular	neoplasia	n.n.
39340	NIH_MGC_100	liver	neoplasia	n.n.
39895	NIH_MGC_102	salivary gland	neoplasia	n.n.
39925	NIH_MGC_110	pancreas	neoplasia	n.n.
39927	NIH_MGC_112	skin	neoplasia	n.n.
39928	human insulinoma	pancreatic islet	u.c.	u.c.
39951	Melton n human islet 4 N4-HIS 1	pancreatic islet	normal	n.
39982	human fetal pancreas 1B	pancreas	normal	u.c.
39995	NIH_MGC_126	pooled tissue	normal	n.n.
40023	NIH_MGC_109	ovary	neoplasia	n.n.
40063	S12SNU216	stomach	neoplasia	u.c.
41049	Hembase; erythroid precursor cells (LCB:cl library)	lymphoreticular	normal	u.c.
41171	Schneider fetal brain 00004	brain	normal	u.c.
41585	NIH_MGC_172	u.c.	normal	n.n.
41586	NIH_MGC_173	u.c.	normal	n.n.
41591	NIH_MGC_184	pooled tissue	normal	n.n.
41605	Homo sapiens neuroblastoma COT 25-n	nervous	neoplasia	n.
41607	Homo sapiens T cells (JURKAT cell line) COT 10-n	lymphoreticular	neoplasia	n.
41609	Homo sapiens HELA cells COT 25-n	cervix	neoplasia	n.
41612	Homo sapiens neuroblastoma	nervous	neoplasia	n.n.
41613	Homo sapiens placenta	placenta	normal	n.n.
41614	NIH_MGC_191	u.c.	normal	u.c.
41615	Homo sapiens fetal brain	brain	normal	u.c.
41617	Homo sapiens B cells (RAMOS cell line)	lymphoreticular	neoplasia	u.c.
41618	Homo sapiens T cells (JURKAT cell line)	lymphoreticular	neoplasia	u.c.
41619	Homo sapiens fetal liver	liver	normal	n.n.
41620	Homo sapiens adult brain	brain	normal	n.n.
41631	FLPRSV	u.c.	u.c.	u.c.

Table A.1: CGAP Libraries Selected as Data Source. This 75 CGAP libraries with reasonable mRNA (EST) number, complexity and distribution were used as data source for our procedure. u.c.) uncharacterized; n.n.) non-normalized; n) normalized; m.t.) multiple treatment.

C	tissue
8	brain
7	lymphoreticular
6	liver
5	lymph node
5	pancreas
4	muscle
4	uncharacterized tissue
4	skin
3	lung
3	placenta
3	ovary
2	eye
2	uterus
2	salivary gland
2	pooled tissue
2	pancreatic islet
2	nervous
1	bone
1	genitourinary
1	stomach
1	vascular
1	testis
1	spleen
1	prostate
1	kidney
1	mammary gland
1	cervix
1	colon

Table A.2: Tissue Distribution of the Selected CGAP Libraries

C	protocol
54	non-normalized
15	uncharacterized treatment
5	normalized
1	multiple treatment

Table A.3: Protocol Distribution of the Selected CGAP Libraries

C	histology
43	neoplasia
30	normal
2	uncharacterized histology

Table A.4: Histology Distribution of the Selected CGAP Libraries

Appendix B

Implementation

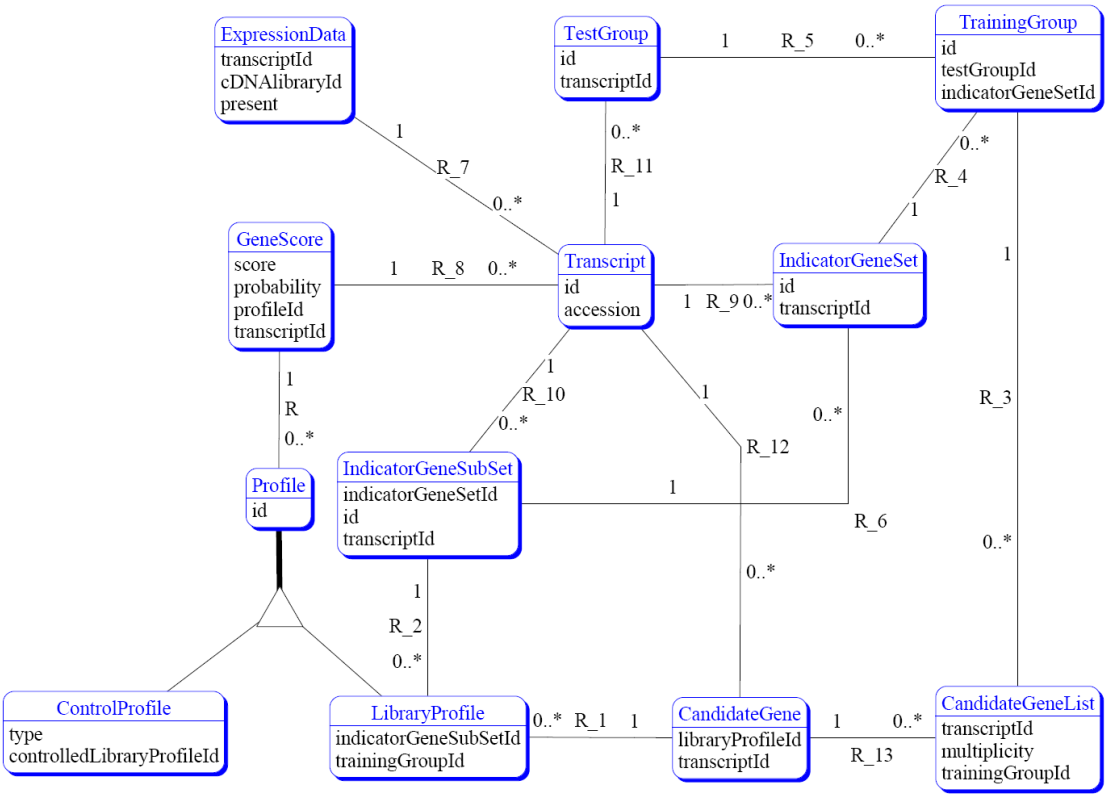

Figure B.1: Entity Relationship Diagram

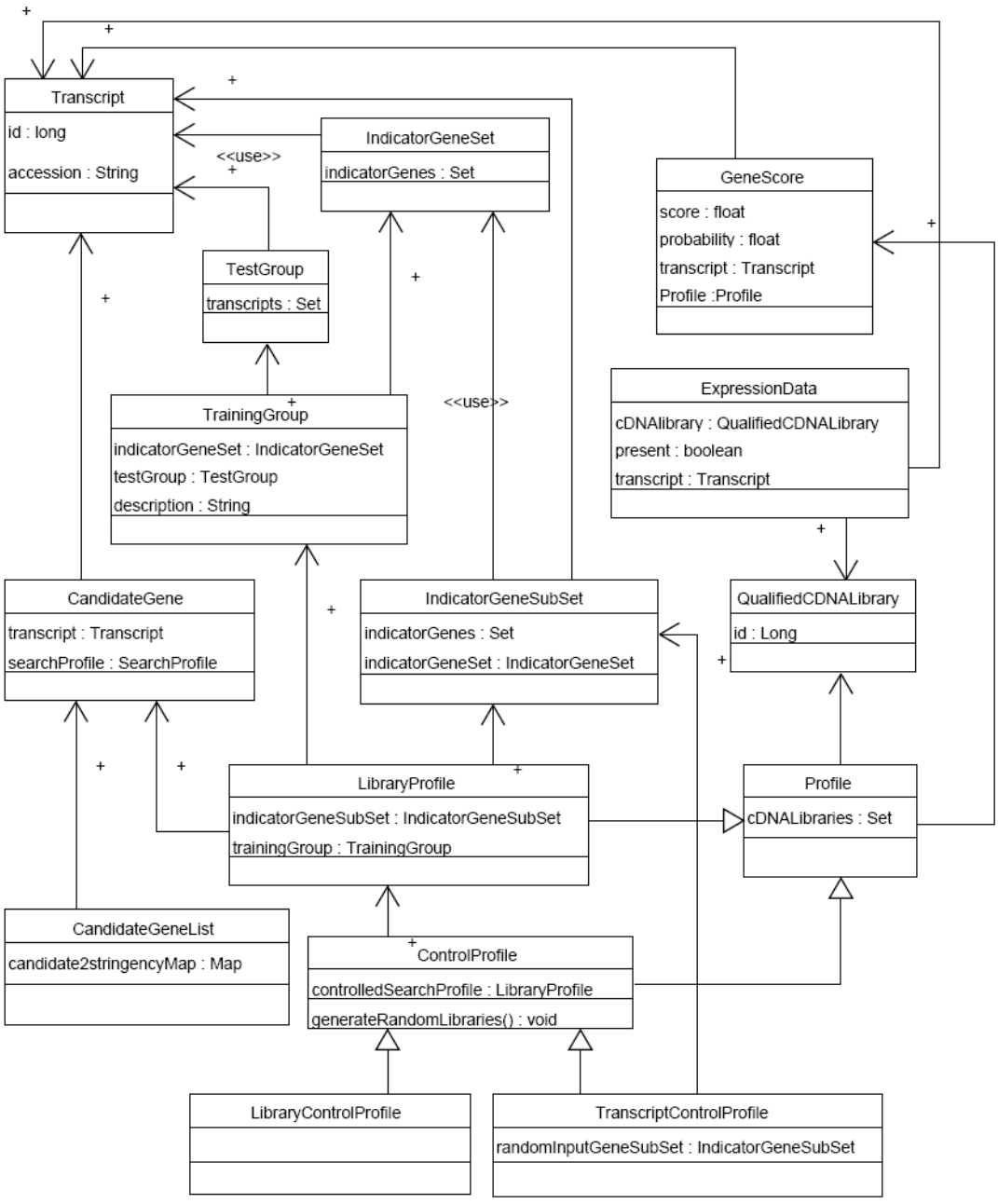

Figure B.2: UML Class Diagram

Anhang C

Anhang gemäß Promotionsordnung

C.1 Erklärung

Hiermit versichere ich, dass ich die vorliegende Doktorarbeit selbstständig verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden.

München, den

C.2 Lebenslauf

Berufserfahrung/Praktika

seit 07/2005 Solution Engineer	Definiens AG, München Automatische Analyse komplexer medizinischer Bilder
5/2005	Klinikum Nürnberg, Medizinische Physik Verbesserung des Workflows in der Strahlentherapie
11/2001 - 02/2005 Doktorand	Xantos Biomedicine AG, München Data Mining von Expressions-Daten zur Akkumulation von angiogenetischen Faktoren Clustering Konzept zur Visualisierung der Zusammenhänge und Abhängigkeiten diverser biologischer Informationen
07/2000 - 02/2001 Diplomand	Friedrich-Alexander-Universität, Erlangen-Nürnberg „Mathematisches Modell der gravitaktischen Orientierung von *Euglena gracilis*"
10/2000 - 12/2000 Praktikant	Mathema Software GmbH, Erlangen Pflege von Daten und Software zur Verwaltung des Trainingsangebots
10/1999 - 02/2000 Werkstudent	Siemens AG, Erlangen Parsen von Excel-Daten in einr MS Access Datenbank
01/1999 - 06/1999 Hilfskraft	Friedrich-Alexander-Universität, Erlangen-Nürnberg Visualisierung von Messergebnissen mit Hilfe von Matlab
07/1995 - 07/1996 Zivildienst	Malteser Hilfsdienst, Nürnberg Ausbilder für Erste Hilfe in der Breitenausbildung

Ausbildung

1996 - 2001	Friedrich-Alexander-Universität, Erlangen-Nürnberg Diplom Mathematik mit Nebenfach Biologie Ø 1,4
1986 - 1995	Willibald-Gluck-Gymnasium, Neumarkt Allgemeine Hochschulreife Ø 2,3 Bundeswettbewerb für Mathematik: 2. Preis in der 1. Runde

C.3 Zusammenfassung

Die vorliegende Arbeit handelt von einem „Data Mining“ Verfahren zur Identifizierung von Genen eines bestimmten Regelkreises bzw. Phänotyps. Das COMMON DENOMINATOR PROCEDURE (CDP) genannte Verfahren basiert auf der Beobachtung, dass Gene, die mit einem bestimmten Pathway/Phänotyp assoziiert sind, häufig zum selben Zeitpunkt am selben Ort exprimiert sind. Eine außergewöhnliche Eigenschaft dieses neuen Verfahrens, im Gegensatz zu bereits bekannten, ist, dass die Spezifität und Wahrscheinlichkeit die gesuchten Pathway/Phänotyp assoziierten Faktoren zu identifizieren mit der Diversität der Eingangsdaten wächst. Es werden drei unterschiedliche Vorgehensweisen diskutiert und miteinander verglichen: (i) elementares CDP, (ii) genetischer Algorithmus basiertes CDP und (iii) Indikatorgen basiertes CDP.

CGAP Expressionsdaten wurden zusammen mit einer definierten Testgruppe angiogenetischer Faktoren benutzt, zur Identifizierung neuer mit Angiogenese-assoziierter Gene. Die Anreicherung von Angiogenese-spezifischen Genen in den resultierenden Kandidatenlisten wurden mit Hilfe (a) der Anreicherung von Genen aus der Testgruppe, (b) der Präsenz von zusätzlichen Genen, deren Angiogenesemodulation bereits beschreiben wurde, und (c) der Präsenz von experimentell validierten Genen, deren Assoziation mit Angiogenese bisher unbekannt war, bewertet. Für alle genannten CDPs konnte eine relevante Anreicherung von Angiogenese assoziierten Genen gezeigt werden.

Das beschriebene Verfahren kann leicht auf andere Pathways/Phänotypen angewandt werden, indem entsprechende TestGruppen, bzw. Indikatorgene definiert werden. Darüber hinaus ist das Verfahren nicht auf CGAP Expressionsdaten beschränkt. Information über die Präsenz von Genen in bestimmten Gewebeproben, wie sie neben EST und SAGE Daten auch RT-PCR, QPCR, Northern Blot und Mikroarray Analysen liefern, ist ausreichend für das CDP. Auf Grund der hohen Spezifität ist das CDP als primärer Screen zur Identifizierung von Targets geeignet. Außerdem kann es mit genomweiten funktionelle Analysetechniken kombiniert werden, um Targets für die Diagnose und Therapie humaner Krankheiten zu finden.